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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,580	04/25/2005	Jin-Hoi Kim	P27726	4797

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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
11/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/532,580	KIM, JIN-HOI	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15,17,19,20,22,24 and 26-61* is/are pending in the application.

4a) Of the above claim(s) *27, 30,32,34,36,39,43,45,48,52,54,57,59,61* is/are withdrawn from consideration.

5)☒ Claim(s) *13,15,17,19,20,22 and 24* is/are allowed.

6)☒ Claim(s) *26,28,29,31,33,35,37,38,40-42,44,46,47,49-51,53,55,56,58 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendments to claims filed on 08/20/07 is acknowledged. In their amendments, claims 14,16,18, 21, 23 and 25 were cancelled. Currently, claims 13,15,17,19, 20, 22, 24, 26-61 are pending. Claims 26-61 were withdrawn as being non-elected subject matter. In response to applicant's amendments dated 8/20/07 render claims 13, 15, 17, 19, 20, 22, 24 allowable. Thus any rejection or objection on claims 13,15,17,19,20,22 and 24 from the previous office action is withdrawn. Applicants have requested that claims dependent upon allowable claims be rejoined. Thus claims 26, 28-29, 31, 33, 35, 37-38, 40-42, 44, 46-47, 49-51, 53, 55-56, 58 and 60 are rejoined and subject to prosecution. The restriction requirement over claims 26, 28-29, 31, 33, 35, 37-38, 40-42, 44, 46-47, 49-51, 53, 55-56, 58 and 60 is withdrawn.

2. The following rejections are necessitated by applicants amendments dated 08/20/07. The amendments resulted in the allowability of claims 13, 15, 17, 19, 20, 22, 24, necessitating the rejoinder of claims 26, 28-29, 31, 33, 35, 37-38, 40-42, 44, 46-47, 49-51, 53, 55-56, 58 and 60.

3. This rejoinder is done because at the present time, there is no burden to search the additional groupings. The restriction requirement may be reinstated at a later date.

4. The rejoinder of the method claims necessitates the following rejections.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 26, 28-29, 31, 33, 35, 37, 38, 40, 41, and 42 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 26, 28-29, 31,33, 35, 37, 38, 40, 41, and 42 recite "an animal's fertilized ovum" and "a transgenic animal" encompassing the expression vectors. The specification teaches that animal of the claimed invention encompasses "all animals that urinate" (see page 13 of the instant specification). These cells and transgenic animals can be in, and read on, a human being, said cells becoming integrated into the human being and therefore an inseparable part of the human being itself. The scope of the claim, therefor, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 26, 28-29, 31, 33, 35, 37, 38, 40, 41-42, 44, 46-47, 49-51, 53, 55-56, 58, and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

8. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter., 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

9. 1) The nature of the invention. The invention involves a fertilized ovum of any animal that urinates, any transgenic animal obtained by the implantation the fertilized ovum of any animal that urinates where the transgene integrates at any point in to the genome and with any copy number of vectors inserts, and methods of making useful proteins comprising making transgenic animals comprising expression vectors driven by a uroplakin II promoter capable of secreting any transgenic protein, including human EPO, into the urine of any transgenic animal. The transgenic fertilized ovum is introduced with the expression vectors using any methodology.

10. 2) State of the art. The art shows that production of transgenic animals that excrete transgenic proteins via the urinary tract is a nascent technology that requires additional development. Zbikowska et al (The use of the uromodulin promoter to target production of recombinant proteins into urine of transgenic animals, Transgenic

Research, 2002. 11:425-435) states that "the major shortcoming of recombinant protein production in the urinary tract is the lack of a reliable and tissue-specific expression vector" (page 425, second column). Zbikowska also teaches that use of the human uroplakin II promoter in transgenic mice expressing human growth hormone showed ectopic expression in the kidney, brain, and testes (page 426, first column). Zbokowska, whose specific embodiments for urinary transgenic expression utilized an alternate Uromodulin promoter, discussed that of the 5 transgenic lines created, suffered from obstacles well known in transgenic animals: uneven production of the transgenic protein between different lines, and that causation of such differences is unknown, (often due to differences of copy number and or site of integration, and only uses mice that are less than 3 months old for experiments (page 432, second column). Zbikowska states that only very low producing lines were able to survive, and that the best transgenic founders/produces died very early, or maybe even during embryogenesis, because of the profound biological activity of the expressed protein. Zbikowska teaches that transgenic models to date expressing EPO have resulted in the development of polycythemia in transgenic mice and rabbits secreting EPO in milk due to ectopic expression of the transgene (see page 433-434), and Zbikowa also reports that the transgenic mice developed by his group developed polycythemia, and states "in the case of EPO which acts at very low concentrations (0.02-0.3 ng/ml of EPO can be detected in human serum of healthy individuals), even small transcriptional or protein leakage appears to be harmful for transgenic animals" (page 434 first column).

11. The examiner is unable to identify any reports of successful transgenic porcine, bovine, poultry, ovine or caprine animals capable of utilizing the uroplakin II promoter driving the human EPO gene in the art. Applicants own post-filing work demonstrates that the development of transgenic animals utilizing the uroplakin II promoter is still a nascent technology. Kwon et al (Cloning and Molecular Dissection of the 8.8 kb Pig Uroplakin II Promoter Using Transgenic Mice and RT4 cells, Journal of Cellular Biochemistry, 2006. 99:462-477) teaches the development of transgenic mice utilizing 8.8 kb of the porcine Uroplakin II promoter, and claims such expression is tissue specific based on analysis of 7 tissues (see abstract, and figures 4 and 5). However, there is no data on additional tissues. Additionally, the authors hypothesize that the tissue specificity is due to insulators, particularly putative PPAR binding sites within the 8 kb promoter but do not actually test this hypothesis in vivo (pages 472-473). Nor are any other transgenic models produced (porcine, bovine, poultry, ovine, and caprine, etc). Furthermore, Kwon teaches "'when producing proteins in the tissues of transgenic animals it is important that the tissue expression the protein is able to execute complex post-translational modification. This process is different from protein to protein and might also vary from tissue to tissue" (page 463).

12. 3) Unpredictability of the art. The art is highly unpredictable. Based on the lack of evidence of successful transgenic development of animals capable of secreting any protein, including EPO, the problems associated with transgenic animals in general, relating to copy number and insertion sites, and that as applicant's work demonstrates, the variability of transgenic animals may vary depending upon the tissue or protein

secreted, a skilled artisan would have to perform undue experimentation in order to successfully make and use the claimed invention.

13. 4) Number of working examples. Applicants have provided a working example of a transgenic mouse expressing human EPO/LacZ gene driven by the Uroplakin II promoter from a fertilized ovum apparently via random insertion into the mouse genome (see examples). Applicants have not provided any working examples of any other transgenic animal, nor have applicants provided the secretion of any other proteins from the urine. Applicants have not assessed as to whether the environment of urine pH effects the stability of any other protein produced by any other transgenic.

14. 5) Amount of direction or guidance present. The applicants provide generic guidance on the production of a transgenic ovum or animal other then a mouse. All actual guidance and direction is directed towards the production of a transgenic mouse. A skilled artisan would conclude, from the instant specification, that the production of a transgenic bovine, would entail the exact same protocol as a transgenic poultry.

15. 6) Level of skill in the art. The level of skill is high. Robl et al (Transgenic animal production and animal biotechnology, Theriogenology, 2007. 67:127-133) teaches that transgenic animals, particularly transgenic live stock is a nascent technology with multiple challenges for broad applicability that till need to be overcome, although they represent a promising field. Robl teaches that pronuclear microinjection of livestock is very inefficient, results in highly variable numbers of copies, and variable expression, and insertion length can result in harmful mutations (see page 127, first column) and the random insertion into an endogenous chromosome causing a mutations is common to

all transgenic methods that rely on random insertion (page 129, column I). Furthermore, developing transgenics with germ line transmission of the transgene is difficult and expensive, due to the lone reproduction cycles of the livestock (page 129, column II). Robl teaches that methods to overcome some of the known obstacles associated with ransom insertion of pronuclear injection in livestock have their own drawbacks: lentiviral vectors have limited insertion size of about 10 kb, and are not capable of forming transgenic animals successfully in monkeys (page 1128, second column through page 129 Ist column), sperm mediate DNA transfer has very low reproducibility and high variability from transgenic to transgenic and species to species (page 129), and michrochomosome transfer also results in a high degree of rearrangement, and low levels of transgene expression are seen in transgenics (page 131). Thus, in light of the lack of guidance from applicants in the specification regarding the generation of transgenic animals, the problems associated with the generation of transgenic animals, including the random integrations of transgenes in the genomes of mouse and live stock, as well as the variability of generations transgenics between species to species, tissue to tissue, as well as protein to protein, the skilled artisan would be formed to perform undue experimentations in order to make and use the invention as claimed.

16. 7) The breadth of the claims. The breadth of the claims are broad. The claims read on any fertilized ovum of any animal that urinates, any transgenic animal obtained by the implantation the fertilized ovum of any animal that urinates where the transgene integrates at any point in to the genome and with any copy number of vectors inserts,

and methods of making useful proteins comprising making transgenic animals comprising expression vectors driven by a uroplakin II promoter capable of secreting any transgenic protein, including human EPO, into the urine of any transgenic animal. The transgenic fertilized ovum is introduced with the expression vectors using any methodology.

17. Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, including the highly unpredictable art, the scarcity of working examples provided by applicant, the lack of guidance by the applicant, and the broad nature of the invention it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 53, 55, 56, 58, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 53, 55, 56, 58, and 60 recite, a method for producing a "useful protein." It is unclear what a "useful" protein is. The specification does not teach what constitutes "useful." Are the proteins strictly the therapeutic purposes? Are they for industrial purposes? Are they for agricultural purposes? What proteins produced by these transgenics would not be useful? Thus a skilled artisan would be unable to determine the metes and bounds of the claimed invention.

Conclusion

20. Claims 13,15,17,19-20, 22, and 24 are allowed. Claims 26, 28-29, 31, 33, 35, 37, 38, 40, 41-42, 44, 46-47, 49-51, 53, 55-56, 58, and 60 are rejected.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/11/05/07

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